PB86-195450

Prenatal Exposure to the Fungicide Dinocap Causes Behavioral Toricollis, Ballooning and Cleft Palate in Mice, but not Rats or Hamsters

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

1986

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1. REPORT NO. EPA/600/J-86/045	2. PB86-195450
4. TITLE AND SUBTITLE: Prenatal Exposure to the Fungicide Dinocap Causes Behavioral Torticollis, Ballooning and Cleft Palate in Mice But Not Rats or Hamsters (Journal Version)	5. REPORT DATE: 1986
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S): LE Gray, Jr., JM Rogers, RJ Kavlock	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS: EPA, Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO. ACSL1A
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Health Effects Research Laboratory (HERL), Office of Research and Development (ORD), U. S. Environmental Protection Agency (USEPA), Research Triangle Park, North Carolina 27711	13. TYPE OF REPORT AND PERIOD COVERED: Journal Article
	14. SPONSORING AGENCY CODE: EPA 600/11

15. SUPPLEMENTARY NOTES

Teratogenesis, Carcinogenesis and Mutagenesis 6:33-43 (1986) January (Issue 1) 1986 Alan R. Liss, Inc.

16. ABSTRACT

The present study is an evaluation of the developmental toxicity of dinocap in three rodent species using an in vivo teratology screen. Our protocol uses postnatal viability, weight gain and morphological and behavioral development through weaning to assess the developmental toxicity of compounds. Dinocap administered orally on days 7 to 16 of gestation to the CD-1 mouse resulted in increased postnatal mortality at 25mg/kg/d (80% in block 1 and 40% in block 2). Many of the treated pups that died during the neonatal period were "ballooned" and had cleft palates. Although there was no treatment related mortality in the 12mg/kg/d dosage group, 7% (15/221) of these mice and 24% (21/85) of the survivors from the 25mg/kg/d dosage group displayed torticollis (a twisting of the neck resulting in an abnormal tilting of the head). These tilted head mice held the head and forepart of the body tilted constantly to one side, both when resting and walking. The tilt was in either direction but was always constant for a given animal; in different mice the angle varied considerably from almost 0 to 30 degrees. Some mice circled repeatedly in one direction in the home cage, others bobbed their heads and did back-flips while others rolled over, always rolling in the same direction. In the hamster, developmental toxicity was seen at (100 and 200mg/kg/d) or near (50mg/kg/d) maternally toxic doses but no behavioral alterations were noted and none of the pups were ballooned.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT: RELEASE TO PUBLIC	19. SECURITY CLASS (This Report): UNCLASSIFIED	21. NO. OF PAGES: 12
	20. SECURITY CLASS (This page): UNCLASSIFIED	22. PRICE

EPA Form 2220-1 (Rev. 4-77)

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EPA/600/J-86/045
JOURNAL ARTICLE

Teratogenesis, Carcinogenesis, and Mutagenesis 6:33–43 (1986)

Prenatal Exposure to the Fungicide Dinocap Causes Behavioral Torticollis, Ballooning and Cleft Palate in Mice, but not Rats or Hamsters

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The present study is an evaluation of the developmental toxicity of dinocap in three rodent species using an in vivo teratology screen. Our protocol uses postnatal viability, weight gain, and morphological and behavioral development through weaning to assess the developmental toxicity of compounds.

Dinocap administered orally on days 7 to 16 of gestation to the CD-1 mouse resulted in increased postnatal mortality at 25 mg/kg/d (80% in block 1 and 40% in block 2). Many of the treated pups that died during the neonatal period were "ballooned" and had cleft palates. Although there was no treatment related mortality in the 12 mg/kg/d dosage group, 6% (14/226) of these mice and 24% (23/96) of the survivors from the 25 mg/kg/d dosage group displayed torticollis (a twisting of the neck resulting in an abnormal tilting of the head). These tilted-head mice held the head and forepart of the body tilted constantly to one side, both when resting and walking. The tilt was in either direction but was always constant for a given animal; in different mice, the angle varied considerably from almost 0 to 30°. Some mice circled repeatedly in one direction in the home cage, others bobbed their heads and did back-flips, while others rolled over, always rolling in the same direction.

In the hamster, developmental toxicity was seen at (100 and 200 mg/kg/d) or near (50 mg/kg/d) maternally toxic doses but no behavioral alterations were noted and none of the pups were ballooned.

This paper has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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The highest dose of dinocap (100 mg/kg/d during days 7–20) used in the rat study produced mild maternal toxicity (reduced maternal weight gain from day 3 to 10 of gestation), but did not alter the postnatal development of this species.

Key words: dinocap, torticollis, mice, teratology, behavior, cleft palate, ballooning

INTRODUCTION

Dinocap is a fungicide used in the control of powdery mildew and as an aid in the control of mites. It consists of a mixture of dinitrooctyl phenyl crotonates, dinitrooctylphenols, mononitrooctylphenols, and a number of minor inactive ingredients [1]. Dinocap is relatively nontoxic to rats, having an oral LD_{50} of 980 mg/kg for males and 1,190 in females [2]. Six-month and two-year feeding experiments with rats showed that dietary concentrations of 2,500 ppm adversely affected survival, and 1,000 ppm retarded growth among male rats [2]. In another study the administration of dinocap in the diet at 104–126 mg/kg/d (about 10% the LD_{50}) to male and female rats for four generations decreased growth rates and reduced offspring survival in the second generation [3]. A report that dinocap is considerably more toxic to mice (LD_{50} = 53 mg/kg) than rats [4] prompted us to evaluate the teratogenic potential of this compound in three rodent species, the rat, mouse, and hamster.

In the current study, we utilized an in vivo teratology screen that relies on postnatal viability, body weight gain, and morphological and behavioral development through weaning to detect potential teratogenic compounds. The results of such a study are intended to provide information that can be used to determine if a standard teratology bioassay or if other postnatal studies are warranted. We have validated this protocol in an earlier study in which the postnatal development of prenatally treated mice was observed through 250 days of age [5]. In that study, over 40 treatments were used, many of which were of known teratogenic potential in mice, and we found a good correlation between the reported teratogenicity of those compounds and the appearance of postnatal developmental alterations [5,6]. We have extended the observation of postnatal development beyond the neonatal period because 1) we found that treatment-induced mortality occasionally occurred near weaning, 2) neonatal growth was not a useful predictor of subsequent growth, and 3) a number of serious morphological abnormalities developed in treated mice that could not be detected in the newborns but were obvious in weanlings (missing lower incisors, missing Harderian glands, hydrocephaly, hyperactivity, and testicular agenesis) [5]. In a few cases, the postnatal data collected after the neonatal period enabled us to detect teratogenic compounds that were without effect during the neonatal period, while in most cases the additional postnatal data allowed us to describe more accurately a compound's teratogenic potential.

MATERIALS AND METHODS

Chemical

The dinocap used in the present experiments was Technical grade with 84% active ingredients (lot 3-83122) supplied courtesy of Rohm and Haas (Spring House, PA). Corn oil was used as the vehicle in all experiments and the compound was administered by gastric intubation. Dosages for the rats and mice were corrected for purity whereas those used in the hamster were not.

Methods: Mouse

Pregnant CD-1 mice (Charles River) were received on day 3 of gestation and housed individually in clear plastic cages (33 × 20 × 13 cm) with heat-treated laboratory grade pine shavings as bedding (Northeastern Prod. Corp., Warrensburg, NY). The mice were maintained at 20–24°C and 40–50% relative humidity on a 12:12 light cycle with lights off at 1800 EST. They were fed Wayne Lab Blox and tap water ad lib. The first block used 150 dams with 30 to 31 per dosage group. Dinocap was administered in 0.2 ml of corn oil on days 7 through 16 of gestation at 0, 6, 12, or 25 mg/kg/d. In the second block, 100 dams were used with 30, 30, and 40 females in the 0, 12, and 25 mg/kg/d groups, respectively. On day 18 of gestation, seven control dams and 13 dams from the 25 mg/kg/d dosage group were killed as part of an extensive standard teratology evaluation that will be reported elsewhere. All of the females in the first block and the remaining females (n = 16, 15 and 15 at 0, 12, and 25) in the second block were allowed to go to term and the numbers of live pups and pup weight were determined on postnatal days 1, 3, 7, 14, 22, and at weaning (day 34—Block 1, day 30—Block 2). At weaning, the general behavioral response to handling was observed, the females were checked for vaginal opening, and in Block 1, on days 35 to 38, the reactive locomotor activity of a number of animals from each dosage group was tested for 1 hour during the day in a figure-eight maze [7]. Four to six mice per litter were randomly selected for behavioral testing with the exception of the highest dosage group where all eight survivors were tested (n = 44, 48, 52, and 8 mice for the 0, 6, 12, and 25 groups, respectively). This behavior was not measured in the second block, being elevated only in mice with torticollis. The placement of rodents in this novel environment initially elicits very high levels of locomotor activity, far above those that would normally occur in the home cage. Each maze is the shape of a figure eight with two blind alleys projecting from the center and contains eight photocell/infrared light emitting diode pairs which are mounted 0.5 in above the floor. Three photocell/LED pairs are located in each half of the figure eight and 1 in each blind alley. As an animal ambulates, infrared light beam interruptions are recorded and displayed by a micro-processor. At weaning the dams were necropsied and the implantation sites were counted. We now routinely use the implantation data to calculate post-implantation losses to analyze for treatment-induced death. This eliminates the contribution of differences in ovulation rates between females to the variability in litter sizes and, hence, reduces the error variance. In the first block at 105 days of age, five control males and six males from the 25 mg/kg/d dosage group were necropsied and body, liver, kidney, lungs, testis, cauda epididymal, seminal vesicle, Harderian gland, and pituitary weights were taken. In addition, in these animals and in all the remaining male and female mice, the kidneys were examined for hydronephrosis and the other organs were examined for gross pathologies.

Methods: Rats

Sixty-two pregnant Sprague-Dawley (CD-Charles River) rats were received and housed individually in clear plastic cages (20 × 25 × 47 cm) with pine shavings as bedding. The rats were kept on a 12:12 light cycle with lights out at 1800 EST, at a temperature of 20–24°C and a relative humidity of 40–50%. They were fed Purina rodent laboratory chow (5001) and given tap water ad lib. There were 20, 21, and 21

rats in the 0, 50, and 100 mg/kg/d dosage groups, respectively. They were dosed on days 7 to 20 of gestation. Maternal weight change was calculated from days 3 to 10 and from days 10 to 20 of pregnancy. The dams were allowed to deliver and the numbers of live pups and pup weight were determined on postnatal days 1, 3, 6, and 30. Diurnal figure-eight locomotor activity data were collected for 1 hour on days 22–24 with 40, 43, and 34 rats in the 0, 50, and 100 mg/kg/d groups. A random sample of the male rats from each dosage group were necropsied at day 35, at which time body, liver, kidney, adrenal, testis, lung, Harderian gland and brain weights were measured.

Methods: Hamster

Fifty pregnant Syrian hamsters were received on day 3 of gestation from Engle labs and randomly assigned to one of five dosage groups. Pregnant animals were individually housed in clear plastic cages (23 × 15 × 45 cm) on pine shavings and maintained at 20–24^{0}C, 40–50% relative humidity on a 14L:10D light cycle with lights out at 1200 EST. They were fed Wayne Lab Blox (Allied Mills) and tap water ad lib. Dinocap was administered at 0, 25, 50, 100, or 200 mg/kg/d on days 8–11 of gestation. Maternal weight was measured during dosing and at parturition. The females were allowed to deliver and the numbers of live pups and pup weight were measured on postnatal days 1 and 5. The general behavior of the animals was observed through weaning. A random sample of the male offspring was necropsied on day 45 when body, liver, kidney, adrenal, testis, seminal vesicle, lung, brain, and Harderian gland weights were taken and the flank gland diameter was measured.

A second experiment was conducted using hamsters in which dams were dosed (8/dosage group) with 50 mg/kg/d of dinocap on days 7 to 14 of gestation. This dose was the highest dose used in the preceeding dose-response experiment that did not result in severe maternal toxicity. The 1-hour figure-8-maze reactive locomotor activity levels were measured at 43–44 days of age in 24 (12 male and 12 female) animals from each group. This behavioral test was conducted during the diurnal phase of the hamsters' activity cycle.

Statistical Methods

The parametric data in this study were analyzed using the General Linear Models (Proc GLM) available in the 1982 edition of the Statistical Analysis System (SAS User's Guide: 1982 edition). The percentage of animals with torticollis were analyzed by computing a normal deviate Z, derived from the normal approximation to the binomial.

RESULTS

Mouse

Dinocap was not maternally toxic as indicated by maternal viability or weight change at the doses used in the present study. There was excessive treatment-independent maternal mortality in the first block across all dosage groups (~30%) due to a technical problem that was corrected in block 2.

There was considerable mortality in the offspring from days 1 to 3 in the 25 mg/kg/d treatment group (Table I). In the first block, the number of pups dropped from 9.17 on day 1 to 1.67 on day 3, while in the second block there were 9.6 pups

TABLE I. Postnatal Effects of Dinocap in the Mouse (Pregnant Mice Were Dosed by Gavage on Days 7–16 of Gestation)

	Dose (mg/kg/d)			
	0	6	12	25
No. litters in postnatal study	23	7	28	21
No. live pups				
Day 1	10.1	10.6	9.4	9.5
Day 3	9.6	10.0	8.9	4.7[a]
Postimplantation death (implants minus day 6 live)	1.08	0.86	1.64	7.0[a]
Pup weight (g)				
Day 1	1.61	1.53	1.53[b]	1.40[b]
Day 3	2.24	2.06	2.13	1.87[b]
Day 6	4.13	3.58	3.97	3.83
Day 14	7.50	7.97	7.59	7.44
Day 21	12.1	11.8	11.6	10.9
Weaning (males)	24.4	24.5	23.4	20.9[a]
Weaning (females)	20.4	21.0	19.5	18.5[a]
Vaginal opening (%)				
Block 1: day 34	93	92	97	75
Block 2: day 30	51	—	34	4[a]

[a]$P < .01$.
[b]Significantly different from controls: $P \leq 0.05$.

alive on day 1 with 6.2 surviving to day 3. Many of the pups that died during the first 3 days PN had "ballooned" gastrointestinal tracts. The "ballooning syndrome" noted in some of the treated pups resulted from the swallowing of air, which eventually filled the stomach and intestines causing extreme abdominal distention (ballooning) (Fig. 1). These pups usually failed to suckle and died. All "ballooned" pups from the high dosage group that were necropsied had cleft palate. One "ballooned" pup was found in the 12 mg/kg/d treatment group. In addition, an analysis of the pooled data from both blocks indicated that the offspring in the 25 mg/kg/d dosage group weighed less than controls at 1 and 3 days of age, but body weights of surviving pups at 7, 14, and 22 days of age were not different from controls. Body weight was reduced in the 25 mg/kg/d group at weaning and vaginal opening was delayed (Table I).

The behavior of the offspring appeared normal until day 21, at which time a number of the mice in the 12 and 25 mg/kg/d groups displayed torticollis (a twisting of the neck resulting in tilting of the head) (Fig. 2). These tilted-head mice held the head and forepart of the body tilted constantly to one side. The tilt might be in either direction, but the direction was constant for a given animal; the angle varied considerably from almost 0 to 30^0. As these animals aged, the behavior of some of the tilted-head mice became more aberrant; some circled repeatedly in one direction, others bobbed their heads and did back-flips, while others would roll over, always rolling in the same direction. At 30 days of age, the tilted-head mice represented approximately 6% (14/226) and 24% (23/96) of the mice in the 12 and 25 mg/kg/d dosage groups.

The figure-eight maze reactive locomotor activity of the treated mice did not differ significantly from the controls (Table II). The activity of the randomly selected tilted-head mice was elevated ($N = 6$) with a mean activity score of 1042 ± 142, $P < .01$ vs the nontilted-head mice ($N = 153$) from all treatment groups. The

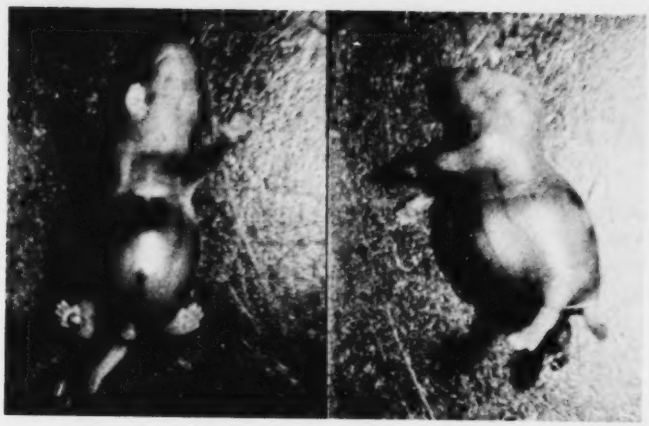

Fig. 1. The administration of dinocap at 25 mg/kg/d on days 7–16 of gestation caused a "ballooning syndrome." The ballooning develops after birth as the pup swallows air, which inflates the stomach and intestine, causing the extreme abdominal distention ("ballooning") seen here.

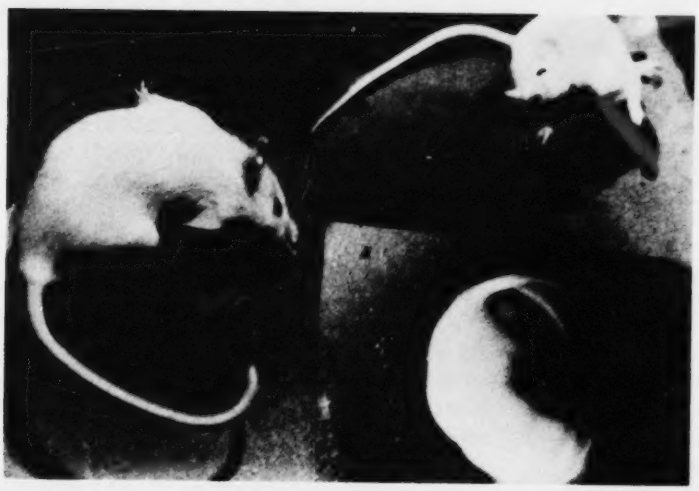

Fig. 2. The picture on the upper right shows the tilted-head posture of a dinocap-treated mouse with torticollis. The same mouse is shown spinning in the lower right and on the left. The picture on the lower right was taken at a slow shutter speed to display the motion and on the left at a faster shutter speed to stop the action.

TABLE II. The Effects of Gestational Administration of Dinocap on the Incidence of Torticollis (Tilted Head) Observed at Weaning and Figure-Eight Maze Activity Levels in Offspring (Data are From Studies Using Rats, Mice and Hamsters)

	Dose of dinocap (mg/kg/d): days 7–16			
	0	6	12	25
Mouse				
Activity levels	822 ± 23 (44)[a]	822 ± 15 (48)	830 ± 26 (52)	841 ± 121 (8)
Torticollis				
% pups affected/ No. observed	0/183	0/53	6[b]/226	24[b]/96
% Litters affected/ No. observed	0/21	0/7	32[b]/28	53[b]/15

	Dose of dinocap (mg/kg/d): days 7–20		
	0	50	100
Rat			
Activity levels	290 ± 19 (40)[a]	265 ± 16 (43)	260 ± 15 (34)
Torticollis			
% pups affected	0	0	0
No. individuals/ No. litters observed	97/12	99/14	87/11

	Dose of dinocap (mg/kg/d): days 7–11				
	0	25	50	100	200
Hamster: Experiment 1					
Torticollis					
% pups affected	0	0	0	0	0
No. individuals/ No. litters observed	75/10	62/10	50/9	42/8	12/2

	Dose of dinocap (mg/kg/d): days 7–14	
	0	50
Hamster: Experiment 2		
Activity levels	409 ± 25 (24)[a]	400 ± 16 (24)
Torticollis		
% affected	0	0
No. Individuals/ No. litters observed	60/7	55/7

[a]Values are $\bar{X}$ ± SE (N).
[b]$P < .01$ greater than control using a Z statistic.

nontilted-head mice had an activity mean of 815 ± 11 counts. The body and organ weights measured in the 25 mg/kg/d dosage group did not differ from the control values and no gross abnormalities were noted in the other mice at this time.

Rat

In the rat, the administration of dinocap at 100 mg/kg/d was maternally toxic as indicated by reduced maternal weight gain from days 3 to 10 of gestation, but offspring viability and weights were unaffected (Table III). Organ weights, including liver, kidney, adrenals, testis, lung, Harderian gland, and brain also did not differ from the control values.

TABLE III. Maternal and Neonatal Effects of Dinocap in the Rat (Pregnant Females Were Dosed With Dinocap on Days 7 to 20 of Gestation)

	Dose (mg/kg/d)		
	0	50	100
Maternal effects			
No. dosed	20	21	21
No. died	3	6	7
No. not pregnant	5	1	3
No. pregnant	12	14	11
Maternal weight gain (g)			
Days 3–10	37.2 ± 1.7	32.3 ± 2.2	29.0 ± 1.8[a]
Days 10–20	110.2 ± 7.0	100.5 ± 4.7	110.4 ± 7.3
Days 3–20	147.5 ± 7.5	132.9 ± 4.3	139.4 ± 6.5
Neonatal effects			
No. live pups			
Day 1	11.5 ± 0.9	9.9 ± 0.8	12.8 ± 0.5
Day 3	11.5 ± 0.9	9.4 ± 0.8	12.5 ± 0.4
Pup weight (g)			
Day 1	6.7 ± 0.2	6.5 ± 0.3	6.4 ± 0.2
Day 3	8.5 ± 0.2	8.6 ± 0.4	8.0 ± 0.3

[a]Significantly different from controls by GLM, $P \leq 0.05$.

None of the dinocap-treated rat offspring displayed torticollis or any of the behavioral abnormalities seen in the treated mice. In addition, figure-eight maze activity was unaffected by the prenatal treatment (Table II).

Hamster

The highest dose of dinocap used in the dose response experiment (200 mg/kg/d) caused four of the ten dams to resorb their litters, and drastically reduced neonatal viability, and retarded growth through day 45. At necropsy, body and organ weights were all significantly lower in the 200 mg/kg/d animals than the control values but no organs appeared specifically affected and no malformations were noted. Pup viability was also reduced in the 100 mg/kg/d treatment group. Pup biomass (total litter weight) was reduced in a dose-related manner on days 1 and 5, with even the two lower doses being significantly affected (Table IV). This indicates that these groups had slightly fewer pups than the control and they weighed slightly less than did control pups.

The administration of dinocap in the second experiment at 50 mg/kg/d on days 7–14 of gestation did not result in maternal toxicity or cause neonatal death, but individual pup weight ($P < .05$) and biomass were slightly reduced (Table V). At necropsy, on day 45 body and organ weights did not differ from the control values. The behavior of the treated hamsters was normal in both experiments, none of the treated pups exhibited torticollis at any time, and the reactive locomotor activity levels of the treated hamsters did not differ from the control values (Table II).

DISCUSSION

The present study describes the effects of prenatal administration of dinocap on postnatal development, using a modification [5] of an in vivo teratology screen that assesses growth and viability in mice on days 1 and 3 [6]. We have adapted this assay

TABLE IV. Maternal and Neonatal Effects of Dinocap in the Syrian Hamster (Pregnant Female Hamsters Were Dosed by Gavage on Days 8–11 of Gestation With Dinocap)

	Dose (mg/kg/d)				
	0	25	50	100	200
Maternal data (all females)					
No. dosed	10	10	10	10	10
No. dead	0	0	0	1	2
No. resorbed	0	0	0	0	4
No. not pregnant	0	0	1	1	1
No. delivering	10	10	9	8	3
Maternal data (dams with viable litters only)					
N	10	10	9	8	3
Maternal weight change					
days 8–11 of gestation	−.23g	−3.19	−5.17	−9.21[a]	−10.73[a]
days 8 gestation to birth	−.14g	−7.48	−2.68	−4.20	−3.43
No. Implantations	13.1	11.4	11.8	10.0	12.0
Neonatal Data					
No. live					
Day 1	9.3	8.8	7.9	7.0[a]	4.3[b]
Day 5	7.5	6.2	6.7	5.2[b]	4.0[b]
Weight (g)					
Day 1	3.04g	2.87	2.87	2.81	2.36[b]
Day 5	6.11	5.96	5.79	5.98	4.95[b]
Biomass (g)					
Day 1	28.3g	25.3	22.5[a]	19.5[b]	10.7[b]
Day 5	45.6	36.7[a]	38.8	31.1[b]	20.6[b]
Post implantation death (implants minus No. live Day 1)	3.8	2.6	4.0	3.2	7.7[a]
Weight (males) (g)					
Day 45					
N	7	—	—	8	7
Body weight	89.9	—	—	88.9	74.8[a]

[a]$P < .05$.
[b]$P < .01$ by GLM and post hoc t-test.

to additional species, the rat and the hamster, and have extended the postnatal observation period, keeping the animals at least until weaning.

Results of the present study demonstrate that dinocap is teratogenic in the mouse, causing cleft palate, "ballooning," and behavioral torticollis (head tilting). The behavioral effects seen at weaning in the offspring from the 12 mg/kg/d dosage group were the only teratogenic effects noted at this dose (Table II). Postnatal growth and viability was normal (Table I) and cleft palate was not detected in any of the pups, demonstrating that the observation of postnatal development of prenatally treated pups through weaning can provide useful information for establishing a NOEL. However, a standard teratologic assessment of dinocap is needed to characterize fully the dose-response relationship of dinocap-induced cleft palate before we can conclude that these behavioral alterations are the only abnormalities seen in the low dosage groups. The lack of a significant effect at 12 mg/kg/d on neonatal viability does not establish that cleft palate is not present in some of the pups in this dosage group. The normal variability seen in litter size among the control litters requires that at least 15% of the offspring die (with an n of 30 per group) for statistical significance,

TABLE V. The Maternal and Postnatal Effects of Dinocap Administered at 0 or 50 mg/kg/d by Gavage on Days 7–14 of Gestation in the Hamster

	Dose (mg/kg/d)	
	0	50
Maternal effects		
No. dosed	8	8
No. died	0	1
No. resorbed	0	0
No. not pregnant	1	0
No. of viable litters	7	7
Maternal weight (g)		
Day 7	114.9 ± 5.7[a]	116.0 ± 6.6
Day 14	134.9 ± 7.2	132.8 ± 6.3
Day of birth	121.6 ± 4.7	119.0 ± 5.5
Day 7 to 14 weight change	20.0 ± 3.7	16.8 ± 2.2
Neonatal effects		
No. live day 1	10.7 ± 0.5	10.9 ± 0.8
No. live day 5	9.4 ± 0.6	9.1 ± 0.4
Weight (g) day 1	2.89 ± .06	2.55 ± .14[b]
Weight (g) day 5	5.55 ± 0.11	5.11 ± .12[b]
Biomass (g) day 1	30.9 ± 1.3	27.4 ± 1.8
Biomass (g) day 5	52.2 ± 2.9	46.1 ± 2.6

[a]Values are means ± SE.
[b]$p < .05$ different from control.

whereas the observation of only a few animals with malformations, like cleft palate in a standard teratology test, or torticollis in a postnatal study, is highly statistically significant. For example, the number of live pups on day 3 is reduced by almost one pup per litter at 12 mg/kg/d (Table I), but this effect is not significant, even with a one-tailed t-test, while the observation that 6% of the offspring are behaviorally abnormal is highly significant ($P < .01$). In an effort to reduce some of the variability, both between and within blocks, we now count the number of implantation sites at weaning in all of our postnatal studies and use this information to calculate treatment-induced postimplantation loss (Table I). This parameter is less variable than the number of live pups in the control dams because the difference from female to female in the number of embryos implanted before treatment is eliminated from the error variance. There is, however, no evidence of an effect on this parameter at 12 mg/kg/d either.

Although we have not previously seen behavioral torticollis (head tilting) in our laboratory, this effect is similar to that described in the pallid mouse mutant [8] and for mouse pups following prenatal deficiency of manganese [9]. The behavioral defects seen in the pallid mice and the manganese deficient mice are due to otolith defects in the inner ear. It is possible that a similar neurological defect may be responsible for the behavioral defect seen after prenatal dinocap exposure.

Dinocap administration during gestation was fetotoxic in the hamster only at or near doses that were also toxic to the dams. It is important to point out that maternal toxicity of the degree seen in this study, or even greater, is not necessarily associated with fetotoxicity in the hamster. In our work on the teratogenicity of endrin [10], we found that in the hamster, postnatal viability and growth of the offspring were similar

to those of the control group even though the dams lost over 18 g during dosing, a maternal effect almost twice as great as that noted in the present study.

In rats, dinocap administered during the latter two-thirds of gestation produced some maternal toxicity, but no effects on the development of the offspring were evident, even at the highest dose. It is possible that higher doses of dinocap than those used in the present study may produce some developmental toxicity, but such an effect would certainly occur concurrent with substantial maternal toxicity.

In the current study, we found that the fetal mouse was more sensitive to dinocap than the fetal rat, an effect that is consistent with the reported species difference in acute toxicity [4]. The mouse is often less sensitive than the rat to teratogenic compounds including nitrofen, cacodylic acid, benomyl, ETU, and the salicylates (Kavlock, personal communication). One reason for this is that the mouse has a higher metabolic rate, enabling it to metabolize and excrete compounds more rapidly. On the other hand, a higher metabolic rate could enhance the sensitivity of the adult and fetal mouse to dinocap, as compared to the rat, if the acute and developmental toxicity are due to the production of a toxic metabolite. This and other possible reasons for the species difference seen are now under investigation.

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